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As a renewal application for this grant will be submitted in the near future, only a brief statement of work completed during the past six months will be submitted at this time. Progress on several new projects which have recently been undertaken will be described in the next report.

The work supported by this grant continues to be directed toward increasing our understanding of the physiology of motivation. Primarily this work involves an analysis of various aspects of approach and escape behavior with techniques involving electrical and chemical stimulation of subcortical structures.

Work referred to in the last report which is now in print:

Elliot S. Valenstein. Independence of approach and escape reactions to electrical stimulation of the brain. J. comp. physiol. Psychol., 1965, 60, 20-30.

Verne C. Cox and Elliot S. Valenstein. Attenuation of aversive properties of peripheral shock by hypothalamic stimulation. Science, 1965, 149, 323.

(Reprints of the above two papers have been forwarded to the Technical Reports Officer.)

We have completed a preliminary draft of a chapter summarizing our investigation of the anatomical locus of reinforcement. This chapter will appear in Progress in Physiological Psychology (Eds. E. Stellar and J. Sprague). Ten copies of this preliminary draft are enclosed.

A paper entitled: "Medial forebrain bundle - lateral hypothalamic area and reinforcing brain stimulation" will appear in the American Journal of Physiology. Reprints of this paper will be submitted when they are available.

The Locus of Reinforcement[1]

Elliot S. Valenstein

Fels Research Institute at Antioch College

I. Introduction and Statement of the Problem

A. Need for a Mechanism of Immediate Reinforcement

With the exception of reproductive activity, there is nothing more essential to survival of the species than the success of animals in approaching that which is beneficial and withdrawing from that which is harmful. It is obviously necessary that mechanisms should have evolved which maximize the likelihood that animals would make contact with the necessities of life and escape from that which was injurious. Such mechanisms may exist at different levels of organization from simple tropistic responses to the learning of complex patterns of adaptive behavior. Adaptive reactions to the environment may vary from relatively fixed reflexes to simple stimuli to the circumspect and circumventing behavior of diplomacy.

We are concerned here with adaptive behavior that is not fixed, but modifiable. In this context, the convenient concepts of <u>reinforcers</u> and <u>reinforcement</u> have been generally adopted. A reinforcer is any event which changes the frequency of occurrence of some preceding behavior. A positive reinforcer increases while a negative reinforcer decreases the frequency of occurrence of the

behavior it influences. The term reinforcer is preferred by many because of the connotation of subjective awareness implied by the words "reward" or "punishment." A reinforcer may be an event that is internal or external to the organism, but in the case of the latter it is generally assumed that there is some internal consequence of the external event. Reinforcers modify behavior by serving as response selectors, encouraging some acts, discouraging others and gradually shaping the characteristics of a response in such a manner that efficiency is increased. Reinforcement is usually operationally defined and therefore makes no committment as to underlying processes. It simply refers to the process, whatever it may be, by which reinforcers exert their action.

Although there is no reason why only one mechanism of reinforcement should have evolved, there has been, nevertheless, a persistent search for a unifying explanatory construct. In recent years, the construct about which most has been written is that reinforcement is based upon a reduction of biological needs or drives. Drive is usually conceived of as the energy force behind behavior and it has been postulated because of the evidence that behavior may be motivated without involvement of tissue needs. Animals may seek out pleasurable sensations that do not fulfill any homeostatic need that has yet been identified (c.f., Morgan, 1957). In a great number of cases, however, there is a close agreement

between the fate of drives and needs. There are good reasons why the idea of a reinforcement process based upon the reduction of needs or drives should have had so many advocates. If an organism is to survive, its behavior should be modified in such a way that biological needs are satisfied. What arrangement could be more convenient than to have behavior guided, that is reinforced, by the consequences of the behavior for biological needs or drive state?

While there is often a close correspondence between the reinforcement process and the reduction of needs or drives there are sufficient instances where these processes do not seem to be correlated. Behavior may be reinforced in the absence of need reduction and even with the intensification of a drive state. Morgan (1957), as well as others, has discussed the shortcomings of a reinforcement theory based solely on the reduction of biological needs and Miller (1963a), who had been one of the strongest defenders of a drive reduction theory of learning, has modified his views recently. The fact that positive and negative reinforcers modify behavior to assure that beneficial stimuli will be approached and nociceptive stimuli be escaped from does not necessitate that behavior be guided by its biological consequences. The existence of such a relationship may only reflect the fact that evolutionary forces have eliminated those organisms so constructed that harmful stimuli functioned as positive, or beneficial stimuli served as negative reinforcers.

A more essential criticism of a theory of behavior modification based upon drive reduction is that changes in the state of the organism are often too delayed to efficiently guide behavior. There now exists considerable evidence that the reinforcement process does not depend upon "feed back" from physiological consequences of the behavior. Sweet substances are ingested and bitter substances are rejected not because of their ultimate beneficial or harmful consequences. These consequences are often too delayed to modify behavior, as it is well established that learning is slow and inefficient when reinforcement is delayed. What is needed is some mechanism to bridge the gap between behavior and the biological consequences of the behavior.

It would seem that one source of immediate modification of behavior results from the fact that stimuli are often not neutral even on first contact. For example, most of the evidence indicates that the reaction to sweet solutions is not learned. In addition to eliciting approach or withdrawal reactions prior to any learning, the pattern of neural responses activated by many stimuli may also elicit pleasurable sensations. Pfaffman has emphasized this aspect of stimulation and has pointed out that "there has been increasing evidence of late that sensory stimulation, divorced from its need or drive reducing concomitants, may function as a reinforcer in its own right" (1960, p. 254). Pfaffman has used the terms "primary reinforcement" and "exteroceptive motivation" to describe his view

that "sensory stimulation, per se together with its ensuing central neural events be considered as a primi determinant of reinforcement" (1960, p. 254). Similarly, Young (1948) has distinguished between appetite, which is based on dietary need, and the palatability of a food stimulus. The latter refers to the hedonic aspects of the stimulus which result in "enjoyment" and "affective arousal" which are experimentally separable from the delayed and remote after-effects of food ingestion. Earlier, he had pointed out that there was a high correlation between pleasantness, beneception and approach behavior and between unpleasantness, nociception and withdrawal (Young, 1936). These relationships do not originate from taste experience alone, but apply as well to other sensory modalities, as for example, olfactory and cutaneous sensations.

We have learned more about the fact that a stimulus may elicit a characteristic response because of its capability to activate specific neural systems. This occurs not only on the reflex level where we are dealing with relatively simple stimuli and responses, but may occur also with complex stimuli and involved reaction patterns. The ethologists have provided us with numerous examples of the latter (Tinbergen, 1951). Work with microelectrode recording techniques has revealed how much of the encoding of afferent stimulation may take place at the receptor level. Early work by Barlow (1953), Hartline (1938) and Kuffler (1953) had shown that different retinal ganglion cells fired in response to either

the onset, offset or onset and offset of flashes of light. More recently, Lettvin et al (1960) and Maturna et al (1960) have demonstrated the existence of specialized visual receptors which respond to such properties of stimuli as convex edge, concave edge, contrast, dark, dimming, direction of movement, etc. Such receptors provide the structural basis for the patterning of the input and the particular pattern would presumably determine the pathway traversed and ultimately the neural structures which are activated. The so-called "bug detectors" which have been shown to respond specifically to small moving objects and not to stationary objects or even to large moving ones trigger the neural pathways for the evocation of the frog's "striking-capture-ingestion" response to a moving fly. Sackett (1963) has suggested that peripheral neural organization may explain the elicitation ("releasing") of many of the fixed action patterns described by the ethologists and the maturation schedule of the receptors may underlie the "critical periods" associated with imprinting.

While most emphasis in the past has been on the capacity of afferent neural patterns to elicit responses we would like to suggest, as has Pfaffman (1960), that such patterns are also capable of direct elicitation of the reinforcement process. For our present discussion we would not emphasize the elicitation of fixed responses, but on the contrary we are considering the process for modifying behavior by encouraging some responses and discouraging

others. We would suggest that this direct elicitation of the reinforcement process by afferent neural patterns, whether they be triggered by exteroceptors or interoceptors, be called "immediate reinforcement." It is conceivable that the more delayed physiological consequences of behavior may also trigger similar afferent neural patterns, but until we are in a position to determine whether this is so, making this temporal distinction may have heuristic value. Immediate reinforcement may have a high correlation with need reduction, but there is no causal relationship. We should make it explicitly clear that our position is not that immediate reinforcement is the only possible reinforcement process, and also that it may have both a learned as well as unlearned basis.

B. Positive and Negative Brain Areas as the Neurological Substrate for Immediate Reinforcement.

It is in this context, we would hold, that the discovery by Olds and Milner (1954) that animals would seek out electrical stimulation of certain brain areas (and consequently self-stimulate) and the discovery by Delgado, Roberts and Miller (1954) that animals would avoid electrical stimulation of other brain areas has the greatest possibility of physiological significance. A number of anecdotes have been told about the "accidental" discovery of the self-stimulation phenomenon. While it is true that there was some element of serendepity with respect to the neural areas eliciting

the effect, it is significant to note that Olds and Milner (1954) were looking for a neural system and a mechanism which would immediately influence behavior (Milner, 1965).[2] Based upon considerations which were similar in some respects to the argument presented here, these investigators believed that a mechanism for immediately encouraging or discouraging behavior was essential. The initial evidence of positive reinforcement elicited by electrical stimulation of specific areas of the rat brain was followed by similar demonstration with the cat (Sidman et al, 1955), monkey (Bursten and Delgado, 1958), guinea pig (Valenstein, 1958), human (Sem-Jacobsen and Torkildsen, 1960), dog (Stark and Boyd, 1961), goldfish (Boyd and Gardner, 1962), bottlenose dolphin (Lilly and Miller, 1962) and rabbit (Cox and Valenstein, 1965). This work demonstrating the ability to elicit reinforcement by direct brain stimulation in this many species attests to the generality of the finding and the possible critical role the phenomenon may play in an evolutionary scheme. To my knowledge no species tested has failed to exhibit self-stimulation behavior from at least some neural sites.

To summarize, the hypothesis advanced here is that in many cases the consequences of an act are often too delayed to serve as an effective guide for behavior. There was a clear need for a mechanism to have evolved which would encourage adaptive behavior and discourage maladaptive behavior directly. The role of immediate reinforcement with its subdivided positive and negative reinforcing

brain systems is to bridge the gap between behavior and its physiological consequences. Evolutionary processes would favor those animals in which the sensory input triggered these reinforcement systems in a way that maximized survival probability for the individual and species.

II. The Anatomical Locus of the Self-Stimulation Phenomenon

A. Background

A number of important questions may be asked about the properties of these reinforcing systems. Among these are problems related to the role of the reinforcing brain system in learning and secondary reinforcement, the interaction of the positive and negative reinforcing systems, the effects of drugs, electrical activity of the brain and autonomic responses associated with the activation of the reinforcing system, the significance of stimulus parameters, the relationship of specific drive states such as hunger and sex to the reinforcing brain system and the anatomical locus of the reinforcing brain system. A recent review article (Olds, 1962) discusses the rapidly accumulating studies that are providing preliminary answers to some of these questions.

We would like to use this opportunity to present some new experimental data relevant to an aspect of the problem of the anatomical locus of the reinforcing system. Several papers have described the distribution of reinforcing sites in different

species, but the rat has been studied most extensively (Olds, 1956; Olds and Peretz, 1960; Olds, Travis and Schwing, 1960; Olds and Olds, 1963). Judging from self-stimulation performance it is clear that positively reinforcing sites are widespread throughout the limbic system, hypothalamus, and to a lesser extent the mesencephalon of the rat brain. There are a number of methodological problems involved in determining the relative reinforcement strength of these positive sites and existing "maps" will have to be continually revised (Valenstein, 1964). Maps based exclusively on self-stimulation, for example, will have to be modified to take into consideration evidence that response rate does not always reflect an animal's preference in a testing situation which permits a choice (Hodos and Valenstein, 1962). Also animals that exhibit only moderate response rates will respond much faster if some of the disturbing side effects of stimulation are reduced by anticonvulsive drugs (Mogenson, 1964; Reid et al, 1964). There are also other properties of reinforcing sites which future maps will have to chart. For example, we have noted that animals with electrodes in anterior hypothalamic sites will frequently self-stimulate at moderately high rates, but often these animals have to be trained to press the lever at the beginning of each session. Without such preliminary training the animals frequently do not press the lever at all. Furthermore, animals that respond at equal rates may differ in the stimulus intensity required to

produce equal performance or they may differ in resistance to satiation (Olds, 1958; Valenstein and Beer, 1964). A recent report has indicated that self-stimulation rates are correlated with other behavior elicited by the stimulation (Plutchik et al, 1966). These "other behaviors" which were studied in the monkey include sexual responses (penis erection), food or water intake, biting, and urination and defecation. It is also clear that the distribution of reinforcing sites are not the same in all species. For all of these reasons, the present mapping of reinforcement centers must be regarded as preliminary.

In spite of the diversity of neural sites which will support self-stimulation behavior, the assumption has been made either implicitly (Fisher and Coury, 1964; Stein, 1964) or explicitly (Olds and Olds, 1964; Morgane, 1964) that the medial forebrain bundle (MFB) and lateral hypothalamic area (LHA) are essential to this phenomenon. Background for this assumption derives from anatomical information stressing the involvment of the MFB in most limbic circuits and its significance as a major pathway to mesencephalic structures including the reticular formation, central grey area and the medial tegmental nuclei of Gudden and Bechterew which have been referred to as the "limbic midbrain area" (Nauta, 1960). Additional support is provided both by the importance of hypothalamic structures for emotional behavior, motivation and visceral reactions (Brady, 1960; Stellar, 1960) and by the brain

stimulation studies which have shown that of all positively-reinforcing regions, the MFB-LHA produces the highest self-stimulation rates,[3] requires the lowest current levels to produce reinforcement and is the most resistant to satiation (Olds and Olds, 1964). More germaine, however, are preliminary reports from lesion studies which have pointed to the importance of this area for self-stimulation behavior. Olds and Olds (1964) have reported that the posterior hypothalamus is essential for reinforcement produced by stimulation of the anterior hypothalamus. Miller (1963b) has described work in his laboratory by Fonberg which indicates that while bilateral lesions in the septal area have no effect on hypothalamic self-stimulation, bilateral lesions in the MFB "virtually abolish responding for self-stimulation via electrodes in the septum." Morgane (1964) has concluded that rats with lesions in the mid-lateral hypothalamic area will no longer work for brain stimulation that was previously highly rewarding and has stated that lesions "anywhere in the trajectory of the medial forebrain bundle result in a motivational inertia."

It would appear that while self-stimulation may be obtained from many sites, some region located in the middle to posterior portion of the lateral hypothalamus plays a central role in positive reinforcement. Presumably this region would be essential because of the capacity to trigger neural and or chemical patterns that increase the probability of repetition of behavior patterns

occuring at the time. Sites other than this lateral hypothalamic area which produce self-stimulation behavior presumably do so by virtue of their capacity to activate this critical region.

B. Some Relevant Experimental Data

1. The Size of the Neural Field Directly Activated by Electrical Stimulation

We have been exploring this problem for several years with a technique which is quite simple. Bipolar stimulating electrodes (Valenstein, Hodos and Stein, 1961) were implanted in a reinforcing area and lesions were systematically placed in pathways and nuclei that were known to be connected to this area. Using various procedures we tested to determine if any changes in reinforcement were produced by these lesions. At the outset of this work it seemed to us that the soundness of this approach depended upon the size of the neural field activated by the electrical stimulus. If stimulation originating from an electrode placed in a given neural area was capable of exciting neural tissue at great distances from the electrode tip, it would be impossible to draw any conclusions about normal anatomical and physiological relationships. There would be little value in interrupting a tract connecting two nuclei of some consequences if the electric field were capable of jumping over the destroyed area and activating intact tissue distal to the lesion. In spite of the fact that the stimulus intensities

necessary for eliciting self-stimulation behavior are often high[4] there are several kinds of evidence which support the position that the neural area activated is restricted to a relatively small area around the electrode tip. Valenstein and Beer (1961) have shown that when bipolar electrodes of the type commonly used in self-stimulation studies (bare of insulation only at the cross-section) were systemically brought closer to an area producing observable behavior (e.g., vocalization or occulomotor responses) the response was produced only when the electrodes were at a distance from the area in the order of a millimeter. This was true even with very high current levels. Stein (1962) has also noted that changing the polarity of a monophasic stimulus with bipolar electrodes produced different results. Presumably even with electrode tips only a fraction of a millimeter apart the location of the more effective cathode was significant. Also relevant to this issue are the findings that different results are obtained from electrodes placed in adjacent structures. Mapping studies, referred to earlier, provide such evidence and indicate that the stimulus does not involve massive activation of large brain areas. In our own laboratory we have also obtained evidence of the importance of the electrode placement as a critical determinant of reinforcing effects (Valenstein, 1965). Figure 1, for example, presents distributions of aversive sites from an atlas being collated by Barbara Case and the author. Behavioral tests of

aversiveness consisted of measuring the efficiency with which animals escaped from the stimulus in a two-chambered testing apparatus which presented the stimulus in one or the other chambers in a random sequence (Valenstein and Meyers, 1964. It is clear from the figure that the placements located in the dorsomedial tegmentum were most aversive. As placements deviated either laterally or ventrally, stimulation was less aversive. Similar evidence for the importance of the neural site stimulated can be provided for placements yielding positive reinforcing effects.

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Figure 1 about here

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There is other experimental evidence that argues for the position that the neural field activated by a bipolar electrode is relatively restricted. Estimates of the area of effective current spread may be derived from studies which place lesions of known size around the tip of the electrode and then testing to determine if intact tissue on the perimetry of the lesioned area can be activated A base line of lever pressing rate was obtained at a number of intensity steps. Following this a small amount of tissue surrounding the electrode tip was destroyed by passing a direct current through the bipolar stimulating electrode. It can be seen in Figures 2 and 3 that the effect of this lesion was to raise the threshold. However, with higher current levels self-stimulation rates comparable to the base line could be elicited. With Rat 5 a second lesion with the same D. C. current intensity produced no

additional change, but with Rat 62 a slightly higher intensity produced a further threshold increase. In both animals, a large lesion produced by passing 2.00 mA of direct current through the electrodes resulted in a complete loss of self-stimulation behavior even at stimulating intensities many times higher than ordinarily used in our laboratory. In the case of Rat 62 the electrode was placed in the lateral hypothalamic area and the electrode was located in the medial septal nucleus of Rat 5. In both, even after the final lesion there was a considerable amount of adjacent tissue, which was known to be positively reinforcing, still intact. In spite of this, it was impossible to obtain any evidence that stimulation was producing positive reinforcing effects. It would appear that the electrical stimulus was not capable of activating this intact tissue.

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Figures 2 and 3 about here

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A similar point was made with a slightly modified procedure. We were concerned that using the stimulation electrode for lesioning might result in a change in electrode characteristics as a result of destroyed tissue forming around and perhaps encapsulating the electrode tip in a high resistance field. Therefore, we burned out an area in the lateral hypothalamus in two animals and the medial septal nucleus in another two animals, and three weeks after the lesion was produced, implanted stimulating electrodes in the center

of the destroyed field. None of these animals could be trained to self-stimulate although we used a range of intensities that included levels several times above that which we normally use. In the septal region, the lateral septal nucleus, a reinforcing area, was left completely intact, but even with these high current levels it proved impossible to elicit self-stimulation behavior. A recent study by Lorens (1965) which we will have occasion to refer to later in more detail, has confirmed our results. Lorens found that the only lesions which abolished self-stimulation behavior were those destroying the tissue surrounding the tip of the stimulating electrode. Hoebel and Teitelbaum (1962) also report that anesthetization or destruction of the tissue under the electrode stopped self-stimulation.

All of the evidence taken together supports the position that with bipolar electrodes, with only the adjacent cross sections at the tips bare of insulation, the neural field activated is relatively restricted. The exact size of the field would, of course, depend upon details of the electrode and stimulus parameters.

2. The Results of Lesion Studies

Having excluded, at least to our satisfaction, the likelihood of any massive spread of current it seemed feasible to ask what neural pathways or centers are essential for the reinforcement obtained from electrical stimulation of the brain. We decided to explore the reinforcement obtained with stimulation of the septal

area. The logic of beginning with this area was somewhat arbitrary, but there were at least two arguments in its favor which seemed to have merit. For the reasons presented above it seemed that if any critical focus for the self-stimulation phenomenon was found it was likely to be in the region of the medial forebrain bundle-lateral hypothalamic area. Placing our stimulating electrodes in the general region which we planned to ablate would present technical problems and possible interpretive problems as well. Of the remaining known reinforcing sites, the septal area seemed to be the area of choice for, excluding the lateral hypothalamus and perhaps the contiguous ventrolateral tegmentum, self-stimulation behavior is most reliably elicited from this area.

In collaboration with Dr. James F. Campbell we placed a series of bilateral lesions, varying in size, throughout the medial forebrain bundle-lateral hypothalamic area. As details of this aspect of the work have been reported elsewhere (Valenstein and Campbell, 1966), only a general description of the results need be provided. Lesions were placed from the more rostral preoptic-anterior hypothalamic region to the more posterior aspects of this system surrounding the mammillary bodies and in the ventral tegmental area of Tsai. In the first experiment of this series we produced moderately-sized electrolytic lesions in the MFB-LHA of 25 albino rats that had received a series of self-stimulation tests at each of three current levels. Stimulating electrodes were all

placed in either the medial septal nucleus or the more anterior medial paraolfactoria area. The surviving animals (N = 19) received two series of post-lesion self-stimulation tests. The self-stimulation tests during the first post-lesion week were somewhat lowered, but within 7 to 10 days all animals responded at rates similar to or higher than those of the pre-lesion tests. Histological analysis revealed that the MFB-LHA was at least partially destroyed on both sides in all cases. Although the amount and portion of the MFB destroyed varied from animal to animal, taking the group as a whole, this system was disrupted from its most lateral to medial extent. As the lesion in any one animal involved less than 50% of the MFB-LHA area, however, we proceded to replicate and extend these findings with destruction of a greater proportion of this system.

In a second experimental group, greater destruction of the MFB-LHA was achieved by inserting the lesion electrode into several areas on each side of the brain. The percentage of animals surviving this extensive damage to the MFB-LHA was not high. Following the production of lesions, many of the animals had severe symptoms of the "lateral hypothalamic syndrome" (Teitelbaum and Epstein, 1962). These animals had poor temperature control, did not groom themselves and refused food. Only by using incubators, force feeding by gastric intubation and highly palatable diets (Rogers, et al, 1965) was it possible to nurse 13 animals to a point where their general vigor and weight approached preoperative levels.[5]

When the animals appeared to be strong enough to withstand a second operation, stimulating electrodes were implanted in the medial septal nucleus.

Preliminary attempts to train survivors to self-stimulate when in a weakened condition met with little or no success. After partial recovery of health, which often took more than a month and in several cases more than two months, these animals could be trained to self-stimulate at low rates. It seemed to us that the rate was low in part because of the still weakened condition of the animals and in part because of hypersensitive reactions to brain stimulation. The latter was manifested by a tendency to self-stimulate best at low current levels, normally an inadequate stimulus for animals with electrodes in the septal nucleus. It was also noted that during this period animals would commonly exhibit the poorest performance at the higher current levels during the first test of each day and then improve over successive tests during the day. At the higher intensities, animals jumped back when stimulated and seemed hesitant to press the lever again. In a number of cases, it appeared that stimulation facilitated recovery of health as animals began to consume more food and water in their home cages after being tested. As the health of the animals improved, their self-stimulation rate increased steadily at the higher intensities and the hypersensitivity to stimulation disappeared. When fully recovered, their response to the lowest

current level was characteristic of intact animals with septal electrodes.

The systematic testing of animals, which began when recovery was judged to be complete, indicated that all animals responded at rates as high or in some cases higher than intact control animals. Histological analysis revealed that between 50 - 90% of the MFB-LHA was destroyed bilaterally. Between animals this amount of destruction was evident at the frontal plane of the preoptic region, anterior hypothalamic nuclei, the dorso- and ventromedial hypothalamic nuclei, the posterior hypothalamic nuclei, the mammillary bodies and the ventral tegmental area of Tsai. A number of the lesions involved significant destruction of the zona incerta, substantia nigra, internal capsule, fornix columns, mammillary bodies and peduncle, and the mammillothalamic tract. Figure 4 presents typical anterior to posterior MFB-LHA lesions from this series of animals.[6]

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Figure 4 about here
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We also determined that electrodes placed more rostrally, in the area around the Tractus olfactorious intermedius, supported self-stimulation response rates only slightly less than those produced with septal electrodes. It was then possible to make coronal knife cuts between the electrode and the MFB-LHA. If the knife cut were made in four stages separated by recovery periods

long enough for animals to regain their preoperative weight a number of animals survived this procedure. The details of the method are presented elsewhere (Valenstein and Campbell, 1966). It is sufficient to indicate that the ventral portion of the forebrain which contains the main connections between the region stimulated by the electrode and the MFB-LHA was severely disrupted. Such animals self-stimulated at rates comparable in all respects to intact control animals with identical placements. Figure 5 presents a typical lesion resulting from the coronal knife cut and illustrates the electrode placements.

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Figure 5 about here
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As a result of this work we have concluded that providing animals are given a sufficient postoperative recovery period there is no portion of the MFB-LHA that is essential for self-stimulation. The reinforcement associated with stimulation of the septal area is not dependent upon the integrity of the MFB-LHA. The only explanation we can offer at this time for the claims that this area is essential for self-stimulation is that animals were not tested for a sufficiently long enough period of time following the production of lesions. Recently, work by Lorens (1965) has completely supported and extended our conclusions. This investigator implanted stimulating electrodes in the positively reinforcing lateral hypothalamic area and proceded to make lesions both rostral and caudal

to the site of the electrode. Rostral lesions transected between 75 and 100 percent of the MFB at the level of the anterior hypothalamic and preoptic area. Caudal lesions in the region dorsolateral to the mammillary bodies and in the ventral tegmental area interrupted the tegmental projections of the LHA to the central grey, midbrain reticular formation and the nuclei of Bechterew and Gudden in the midbrain. Neither animals suffering the rostral or caudal lesions exhibited any significant change in self-stimulation performance. Lorens also produced "combination lesions" involving both rostral and caudal projections of the MFB. In such preparations the MFB connections from the electrode site to the preoptic area and basal telencephalon and to the tegmentum were "virtually destroyed," but such animals continued to self-stimulate with no significant change in response rate. Some lesions produced complex effects such as altering the preferred duration of stimulation, but the major conclusion of these experiments, as of with ours, was that self-stimulation does not depend upon the integrity of the MFB. While our results were based upon animals with septal electrodes, Lorens' data were collected with animals with LHA electrodes. The conclusion is therefore broadened to include the two most commonly studied reinforcing brain areas.

The work on the MFB-LHA indicated that this system, which appeared to be the most likely candidate for a critical focus for the self-stimulation phenomenon, was not essential. There was

still the possibility that a critical focus existed in some other neural structure. Therefore, we have extended our work on the anatomical locus of the reinforcing properties of septal stimulation by lesioning other neural areas commonly implicated in the regulation of limbic system functioning.

In addition to the ventral projection from the septal area through the MFB, the septal area also projects dorsally to the hippocampus by way of the fimbria-fornix system. We have placed lesions in the fimbria-fornix and dorsal hippocampus and have seen no evidence of any decrement in self-stimulation performance. In fact, although it has not been consistently observed, we have often seen dramatic increases following such lesions. Figures 6 and 7 illustrate two cases in which there has been considerable disruption to the dorsal hippocampus and fimbria-fornix and the self-stimulation rate was significantly above that characteristically seen with septal electrodes.

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Figures 6 and 7 about here
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These animals achieved average lever pressing rates of 87 and 99 responses per minute on a reinforcement schedule which provided a 0.5 second stimulus train for each lever press unless the stimulus was already on. The animals responded with the rapid pattern typical of animals with lateral hypothalamic electrodes. Normally animals with septal electrodes exhibit a pause after each

reinforcement, which seems to reflect neural after-discharge. Electrical recording studies have also indicated the presence of after-discharge (Newman and Feldman, 1964; Porter et al, 1959). The high response rates and the absence of pauses following stimulation seen after lesions of the fimbria-fornix and dorsal hippocampus suggest that the after-discharges with septal stimulation may be triggered in the hippocampus, which has a propensity for rhythmical activity (Liberson and Cadhilac, 1953; Green and Arduini, 1954). These data also indicate that the seizure activity is not a necessary component of the reinforcement, a question about which there has been some speculation, but may actually interfere with performance. Bogacz et al, (1965) have also pointed out that the reinforcement resulting from brain stimulation may be dissociated from epileptiform activity. These investigators have noted that the very high self-stimulation rates seen with ventrolateral tegmental electrodes produced no epileptiform discharges and the random spikes seen with posterior lateral hypothalamic electrodes were unrelated to self-stimulation performance. Self-stimulation with septal electrodes produced organized epileptiform after-discharges which "caused" self-stimulation performance to cease for a few seconds during and after the discharge. Even with septal electrodes, however, the thresholds for self-stimulation and after-discharge activity were independent. This is consistent with studies by Reid et al (1964) and Mogenson (1964) who used

anti-convulsant drugs to suppress after-discharges and reported faster self-stimulation rates.

Figures 6 and 7 illustrate, in addition, considerable damage to the cingulum, stria medullaris, anterior thalamic nuclei and dorsal thalamic area. Other lesions produced in our laboratory have also involved these structures as well as the habenular with no evidence of any decrement in performance. Asdourian et al (1966) has also found that lesions of the dorsal hippocampus and thalamus do not seem to interfere with self-stimulation performance. Although these authors could find no consistent correlation with site of damaged area, approximately 50% of their lesioned animals exhibited significant increases over preoperative levels. Similarly, Lorens (1965) noted that his rats with electrodes in the lateral hypothalamus showed a significant increase in self-stimulation rate following destruction of the septal area. In the light of our discussion of after-discharges being the probable cause of the slower response rates seen with septal electrodes and the evidence for the dissociation of reinforcement and epileptiform activity we would conclude that the dorsal hippocampus plays no essential role in the self-stimulation phenomenon. The recent report that hippocampal ablation studies implicated this structure in the regulation of approach and withdrawal function (Grastyan et al, 1965) apparently does not apply to the approach behavior seen with activation of the positive-reinforcing brain system.

Figure 8 illustrates a large bilateral lesion which involved the amygdala nuclei and the ventral hippocampus. These animals self-stimulated at a rate that was above the average of intact animals with septal electrodes. It would appear that these structures are not critical either.

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Figure 8 about here
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In our search for a critical focus we have also produced midbrain lesions. Figures 9 and 10 illustrate two cases of extensive damage to the central grey and the adjacent medial portion of the reticular formation. These animals self-stimulated at the rate of 95 and 70 responses per minute, respectively, rates which are clearly above that normally seen with septal animals. Lorens (1965) has reached a similar conclusion with animals self-stimulating with lateral hypothalamic electrodes. He reports that central grey lesions failed to produce any significant effect on self-stimulation performance while lesions of the midbrain reticular formation produced a significant increase in the total amount of stimulation obtained by animals in testing sessions.

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Figures 9 and 10 about here
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To be added to the picture that is emerging are two earlier studies by Ward. This investigator has reported that basal tegmental (adjacent to the interpeduncular nucleus) self-

stimulation is unaffected by either amygdaloid and overlying lateral and inferolateral cortical lesions (Ward. 1961) or ablation of the septal area with involvement of the cingulum, hippocampal and anterior commissures, fornix columns and diagonal band of Broca (Ward, 1960). Also Wasden (1964) and Reid and Porter (1965) have ablated frontal and other cortical areas and have found no region which is crucial to the reinforcing effect obtained with electrical stimulation of the lateral hypothalamus. The latter investigators also ablated the septal area, medial dorsal caudate and the anterior preoptic area and found no decrement of self-stimulation performance with posterolateral hypothalamic electrodes. The anterior preoptic area lesions seem to produce enhanced self-stimulation performance in most of the animals. These investigators also report that lesions of the amygdaloid area did not produce any change in self-stimulation with electrodes in the septal area.

III. Some Summarizing Remarks and Speculations

In summary, several major points in this presentation should be stressed. We have indicated that there are strong arguments against a simple drive reduction theory of learning because of the many instances where physiological effects are too delayed to provide the adequate temporal conditions for reinforcement and learning. Furthermore, there are stimuli which have reinforcing consequences which do not reduce biological needs or drives in any

known way or may even increase drive states. The modification of behavior to assure more efficient escape from harmful and approach to beneficial situations and the maximizing of survival probability in general would require the evolving of some mechanism for immediately facilitating or inhibiting behavior. The suggestion has been offered that this mechanism be called immediate reinforcement. We have noted that reinforcing brain structures exist in all vertebrate animals in which they have been looked for. Providing the self-stimulation phenomenon does not rest upon some as yet undetected artifact and granting the importance of a mechanism for immediately facilitating or inhibiting momentary behavior it would appear likely that those neural structures which produce reinforcing effects when stimulated may be involved in such a mechanism.

In exploring the subject of the anatomical locus of reinforcement we have been concerned with questions about the nature of the functional organization of this system(s) and with a search for some structure or pathway that might be considered to be a critical focus. It was pointed out that while the precise charting of structures which can produce self-stimulation is quite complex, there is sufficient evidence that the electric stimulus does not massively involve large areas of the brain. While many structures will exhibit reinforcing effects, the placement of the electrode is a critical determinant of the reinforcing effect produced. There does not appear to be any massive spread of stimulating current to

neural areas located at any great distance from the electrode tip.

Although the area stimulated is the critical determinant of any ensuing reinforcing consequences, the relationship with other parts of the nervous system appears to be massive and diffuse. It seems to us that any search for a critical focus or essential pathway for the self-stimulation phenomenon will meet with little success. We have summarized evidence which indicates that extensive destruction of major limbic and midbrain structures and pathways does not eliminate self-stimulation. The little contrary evidence has not been reported in detail to date and seems to us to occur with animals that have not been tested for a sufficiently long time following the production of the lesions, rather than from any interference with the reinforcement process. Where sufficient time and effort have been expended to restore the lesioned animals to a reasonable state of health no deficit in performance was seen. It would probably not be possible to destroy all major limbic pathways in the same animal, but attempts to place lesions both anterior and posterior to the stimulating electrode have not produced any significant change.

The fact that self-stimulation is not abolished by such large and varied lesions throughout the limbic system and midbrain area may be considered by some to indicate that the phenomenon rests upon some undetected artifact. The conclusion which seems to us to be consistent with the data is that <u>the neural substrate</u>

for the self-stimulation phenomenon is characterized by massive redundancy and possibly also a plasticity which provides a basis for reorganization. It is, of course, a huge and dangerous jump from the data on positive and negative reinforcement with brain stimulation to the concept of reinforcement in general. To the extent that the jump is justified, these conclusions would apply in general.

Speculation about the physiological basis for this plasticity must go beyond the present frontiers of our knowledge. We have been assuming all along that it makes no sense to think of reinforcement as being localized in a given structure. Localization is important only as a means of indicating that a process may be initiated (or blocked) by experimental manipulation of a so-called "center." The concept of "centers" for the self-stimulation phenomenon must rest on the evidence that the reinforcing effects of brain stimulation are critically dependent upon the neural structure activated and the fact that these structures must be intact in order for the reinforcement effects to be produced. There is no evidence, although no one has looked for it, that following destruction of reinforcing sites new areas not previously reinforcing acquire this property. Indeed, the little available evidence suggests that it is difficult to modify the reinforcing consequences of stimulating a specific structure (Valenstein, 1965). Plasticity as we have used the term refers not to the areas capable

of initiating the reinforcement process, but to the anatomical substrate for the spread of this process.

The evidence presented is antagonistic to any notion of fixed and essential neural pathways. One is reminded of Herrick's (1957) comments on the neurological substrate of inherited reflex patterns and "integrative nervous functions." The former, according to Herrick, is dependent upon "permanently linked chains of conductors," while the latter utilizes the more pliable tissue of the neuropil, a "fabric of relatively unspecialized nerve cells and very thin fibers, within which there are no well-defined tracts of fibers." The neuropil is widely distributed throughout the central nervous system and Herrick believed it was responsible for "the more total or organismic functions of tonicity, summation, reinforcement, facilitation, inhibition . . ." The action of the neuropil, he wrote, is "not inflexibly tied to any particular nerve cells and fibers. They can use any appropriately organized tissue that is not already specialized for some specific function."

Whether it is the neuropil or some other functional elements within the nervous system that are responsible for this plasticity we are not yet in a position to determine. The fact that self-stimulation is not abolished by massive destruction of major neural pathways may suggest that some kind of humoral transmission is at work. There is the possibility that such a mechanism will be discovered to play a role in the self-stimulation phenomenon.

From our present vantage point humoral transmission would appear to be too slow to reinforce responses occurring from moment to moment, but it is conceivable that we may have assumed this to be true without sufficient evidence.

If the substrate responsible for the spread of the reinforcement process is in doubt, answers to the question of what it is that is spreading are even more uncertain. The process is more complex than that which would be involved in either an excitatory or inhibitory influence. Positive and negative reinforcement both produce an excitation which energizes behavior. The behavior which results may represent an acceleration of what is going on or a substitution of antagonistic behavior, as for example that seen when an animal switches from approach to withdrawal responses. The process must be encoded in some way to serve as a "response selector." Herrick (1948) clearly recognized this when writing about the olfactory sense of mammals when he noted that lacking any localizing function of its own it is responsible for "the activation or sensitizing of the nervous system as a whole and of certain appropriately attuned sensori-motor systems in particular, with resulting lowered threshold of excitation for all stimuli and differential reinforcement or inhibition of specific types of responses." As most of the positive reinforcing sites are located in areas believed to be related to the olfactory sense in lower florm, Herrick's comment seems particularly appropriate.

It is difficult to resist the temptation to point out that the reticular formation with its capacity for inhibiting or exciting specific responses as well as influencing general organismic states may play a key role in the differential reinforcement process. The reticular formation lesions which were reported in this paper to have little influence on self-stimulation behavior were all located in rostral regions. Perhaps we must search again more caudally. Clearly we have left some problems for others to solve.

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Footnotes

1. Supported by NIH research grant M-4529, Career Development Award MH-4947, and NASA research grant NsG-437.

2. I have not had the opportunity to discuss the rationale for the initial work with aversive brain stimulation with the authors.

3. In a recent paper (Bogacz et al, 1965) the ventrolateral tegmental area produced higher self-stimulation rates than that produced by the lateral hypothalamus.

4. The actual intensities necessary, of course, depend upon the configuration of stimulus parameters and reinforcing site. With brief pulse and train durations higher current levels are required. However, within a neural site the energy of the stimulus as measured in coulombs seems to be the critical factor (Ward, 1959).

5. The success of this part of the project was due to the dedicated work of Thelma Valenstein, who also performed some of the surgery and subsequent testing of animals.

6. The author would like to express his debt to Barbara Case and Ruth Campbell for their most competent assistance with the histological preparation.

Figure Legends

Figure 1. Distribution of very aversive and moderately aversive sites in the tegmentum of rats tested in our laboratory (after Koñig and Klippel, 1963). Data collected from two-chambered testing apparatus which is equally suitable for demonstrating approach or escape behavior (Valenstein and Meyers, 1964). Note that the most aversive sites (highest escape efficiency percentage) are located in the dorsomedial tegmentum. Sites deviating either ventrally or laterally are less aversive. Question mark indicates the electrode site in an animal that changed from a high to a moderate escape efficiency during the course of the testing schedule.

Figure 2 Average self-stimulation rate of animal with electrode in the medial septal nucleus at different stimulus intensities before and after production of lesions around tip of stimulating electrode. Note that the second lesion which was produced by passing the same destructive current through the electrode as used with the first lesion resulted in no further increase in threshold. The third larger lesion completely eliminated self-stimulation behavior.

Figure 3. Average self-stimulation rate of animal with electrode in the lateral hypothalamic area at different stimulus intensities before and after production of lesions around tip of stimulating electrode. Each progressively larger lesion increased the threshold. The third lesion completely eliminated self-stimulation behavior.

Figure 4. Representative anterior to posterior lesions of the medial forebrain area. Solid black line encloses area of greater than 90% destruction of cells and fibers. Sections selected to illustrate bilaterality of lesion. Actual destroyed area on each side involved larger cross-sectional areas and a minimum of 1-2 mm anterior-posterior extent. Numbers in parenthesis are average self-stimulation rates per minute at current intensity producing best performance. Averages were based on last 5 tests (after Valenstein and Campbell, 1966).

Figure 5. (A) Paraffin embedded section illustrating tissue damage resulting from coronal cut with opthalmic knife (see text). Solid black line encloses area of greater than 90% destruction of cells and fibers. (B) Location of electrode tips in experimental (circles) and control (squares) animals.

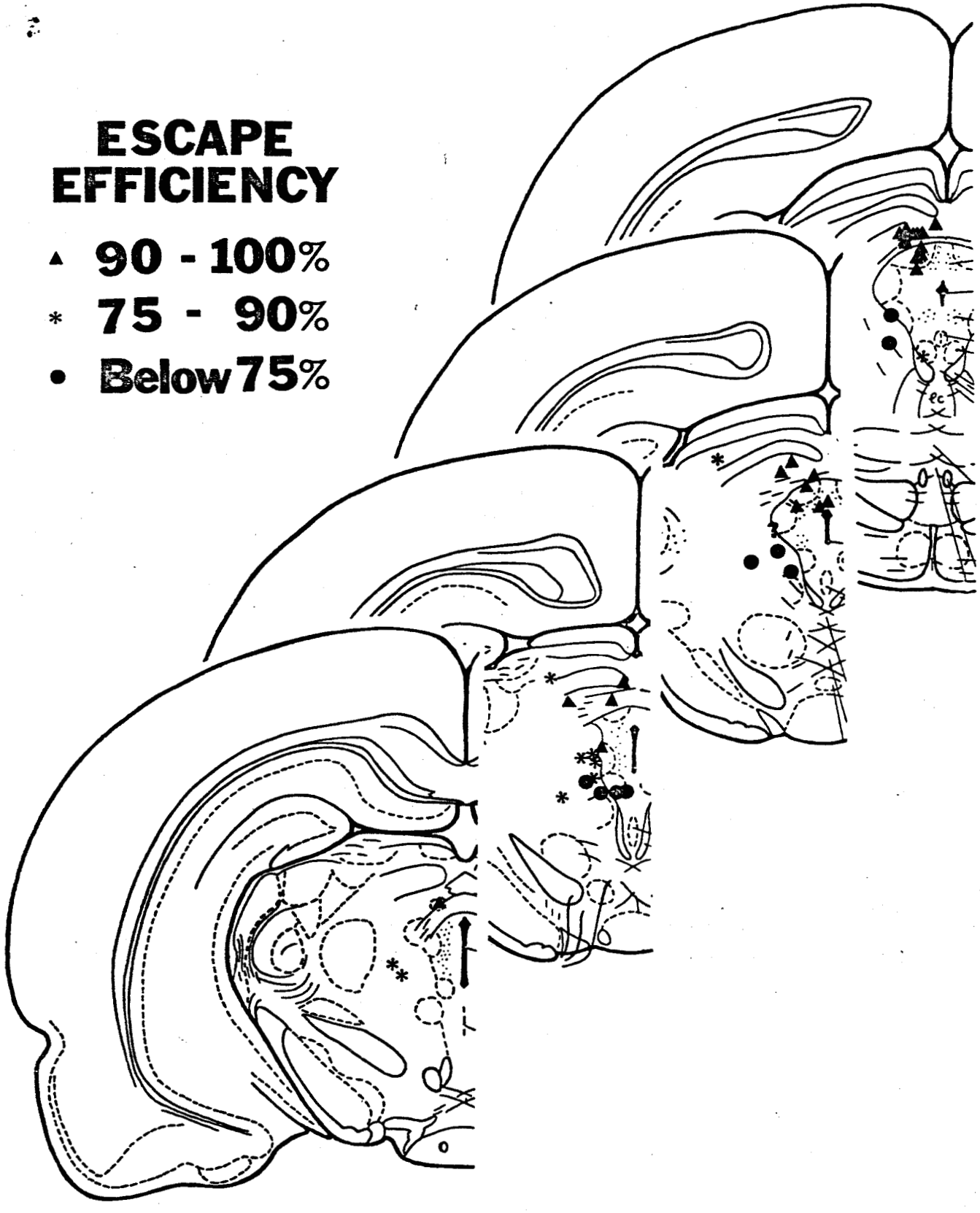
Figure 6. Representative lesion of the fimbria-fornix and dorsal hippocampus. Solid black line encloses area of greater than 90% destruction of cells and fibers. Section selected to illustrate bilaterality of lesion. Actual destroyed area on each side involved larger cross-sectional areas and a minimum of 1-2 mm anterior-posterior extent. Number in parenthesis is average self-stimulation rate per minute at current intensity producing best performance. Average was based on last 5 tests.

Figure 7. Representative lesion of the dorsal hippocampus. Solid black line encloses area of greater than 90% destruction of cells and fibers. Section selected to illustrate bilaterality of lesion. Actual destroyed area on each side involved larger cross-sectional areas and a minimum of 1-2 mm anterior-posterior extent. Number in parenthesis is average self-stimulation rate per minute at current intensity producing best performance. Average was based on last 5 tests.

Figure 8. Representative lesion involving amygdala and ventral hippocampus. Solid black line encloses area of greater than 90% destruction of cells and fibers. Sections selected to illustrate bilaterality of lesion. Actual destroyed area on each side involved larger cross-sectional areas and a minimum of 1-2 mm anterior-posterior extent. Number in parenthesis is average self-stimulation rate per minute at current intensity producing best performance. Average was based on last 5 tests.

Figure 9. Representative lesion involving central grey and adjacent portion of the reticular formation. Solid black line encloses area of greater than 90% destruction of cells and fibers. Section selected to illustrate bilaterality of lesion. Actual destroyed area on each side involved larger cross-sectional areas and a minimum of 1-2 mm anterior-posterior extent. Number in parenthesis is average self-stimulation rate per minute at current intensity producing best performance. Average was based on last 5 tests.

Figure 10. Representative lesion involving central grey and adjacent portion of the reticular formation. Solid black line encloses area of greater than 90% destruction of cells and fibers. Section selected to illustrate bilaterality of lesion. Actual destroyed area on each side involved larger cross-sectional areas and a minimum of 1-2 mm anterior-posterior extent. Number in parenthesis is average self-stimulation rate per minute at current intensity producing best performance. Average was based on last 5 tests.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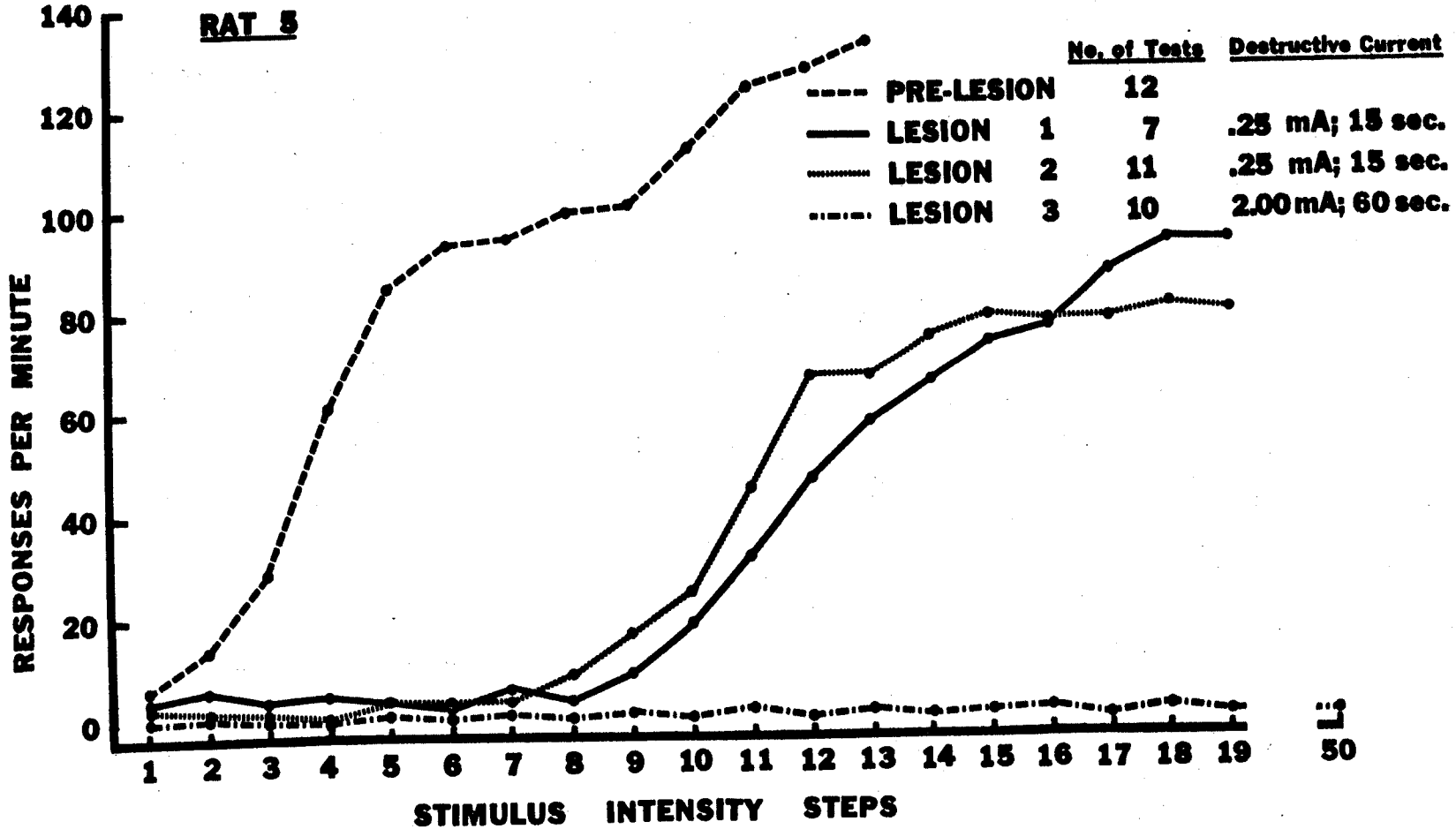
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Destructive Current
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LESION 2 11 .25 mA; 15 sec.
LESION 3 10 2.00 mA; 60 sec.
RESPONSES PER MINUTE
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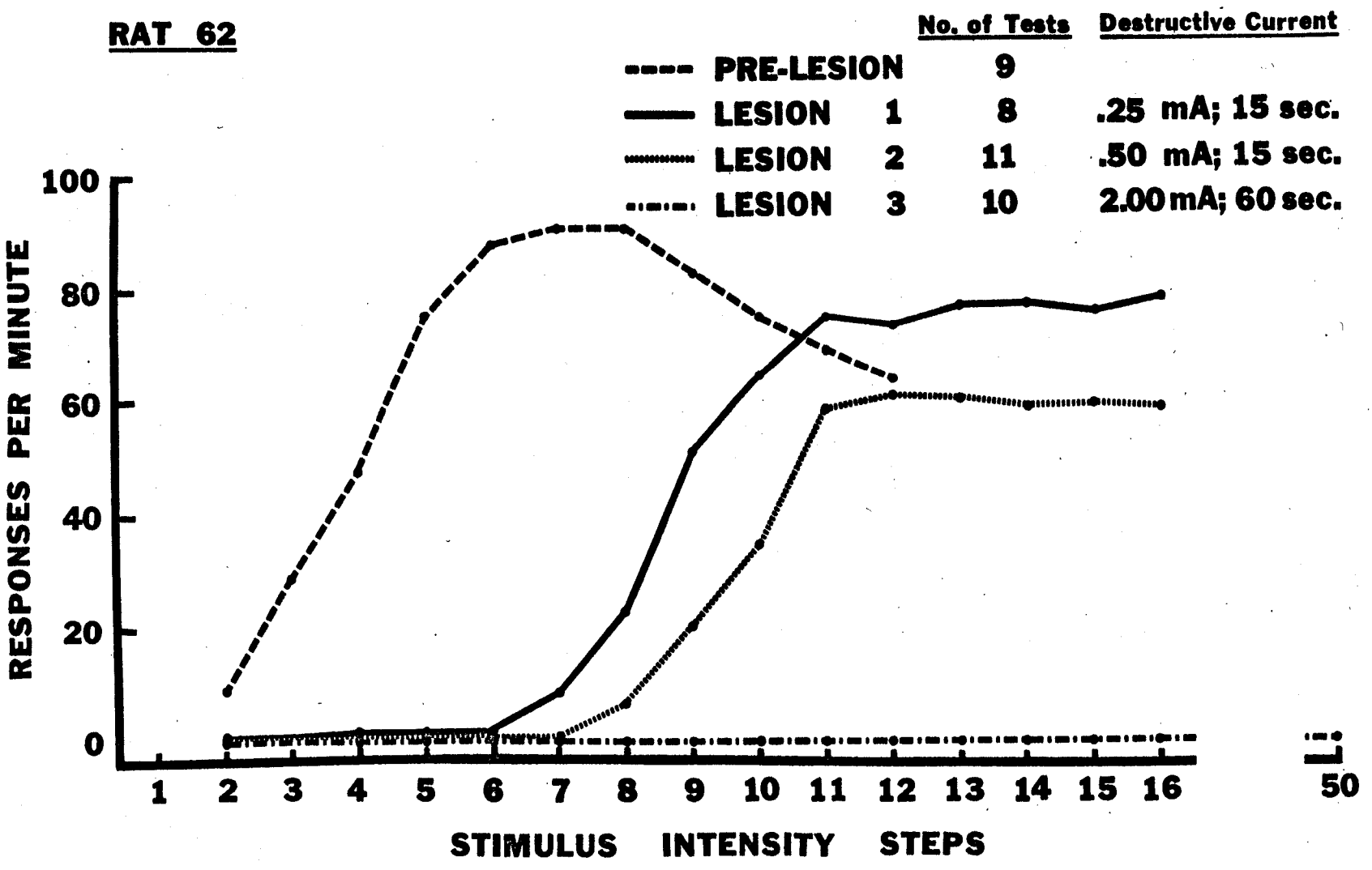
STIMULUS INTENSITY STEPS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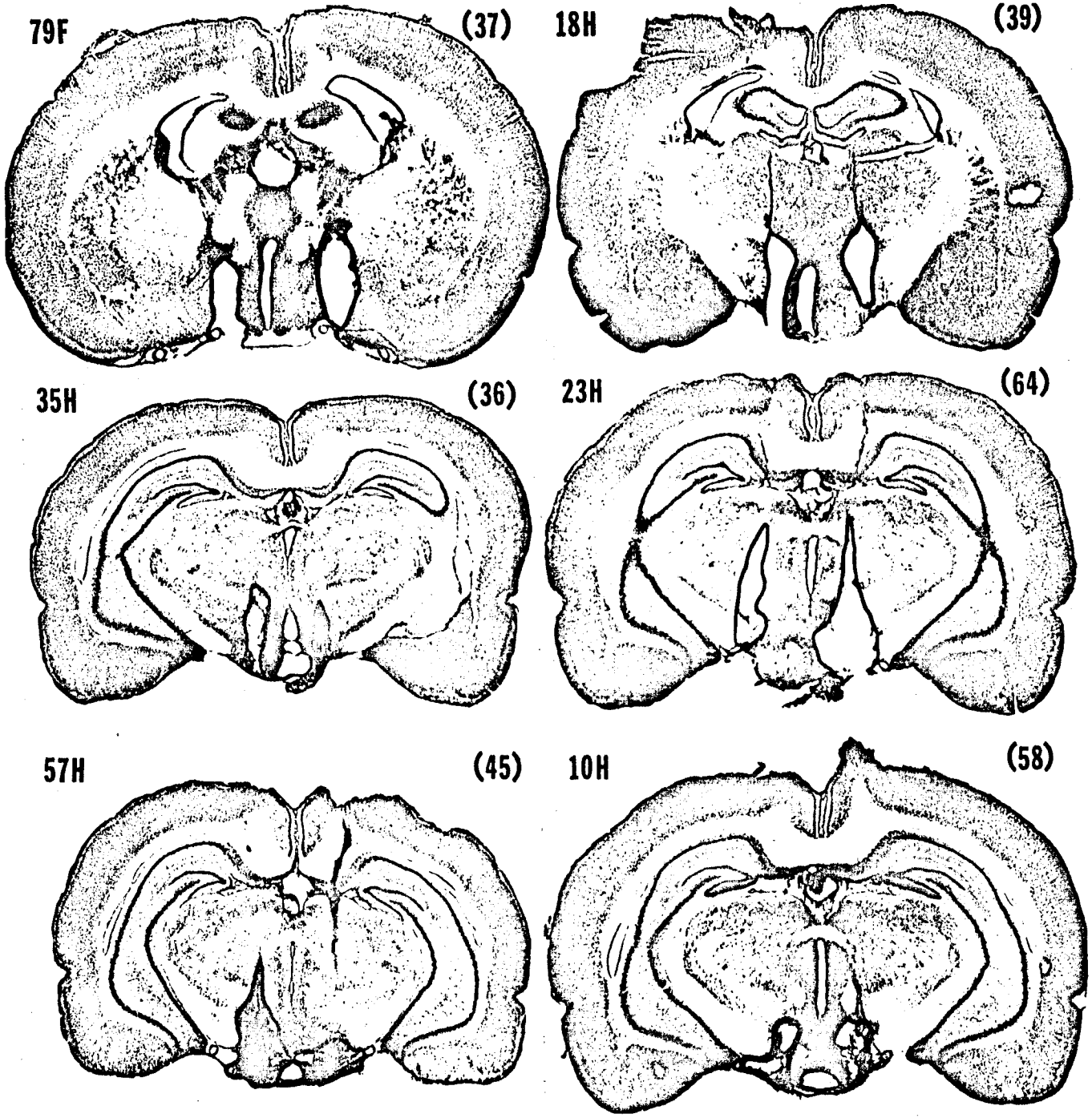
STIMULUS INTENSITY STEPS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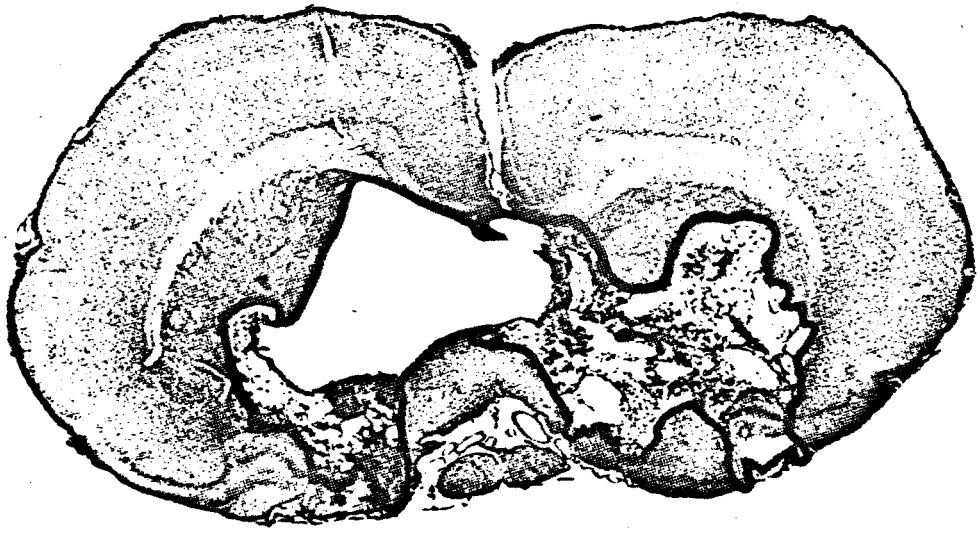

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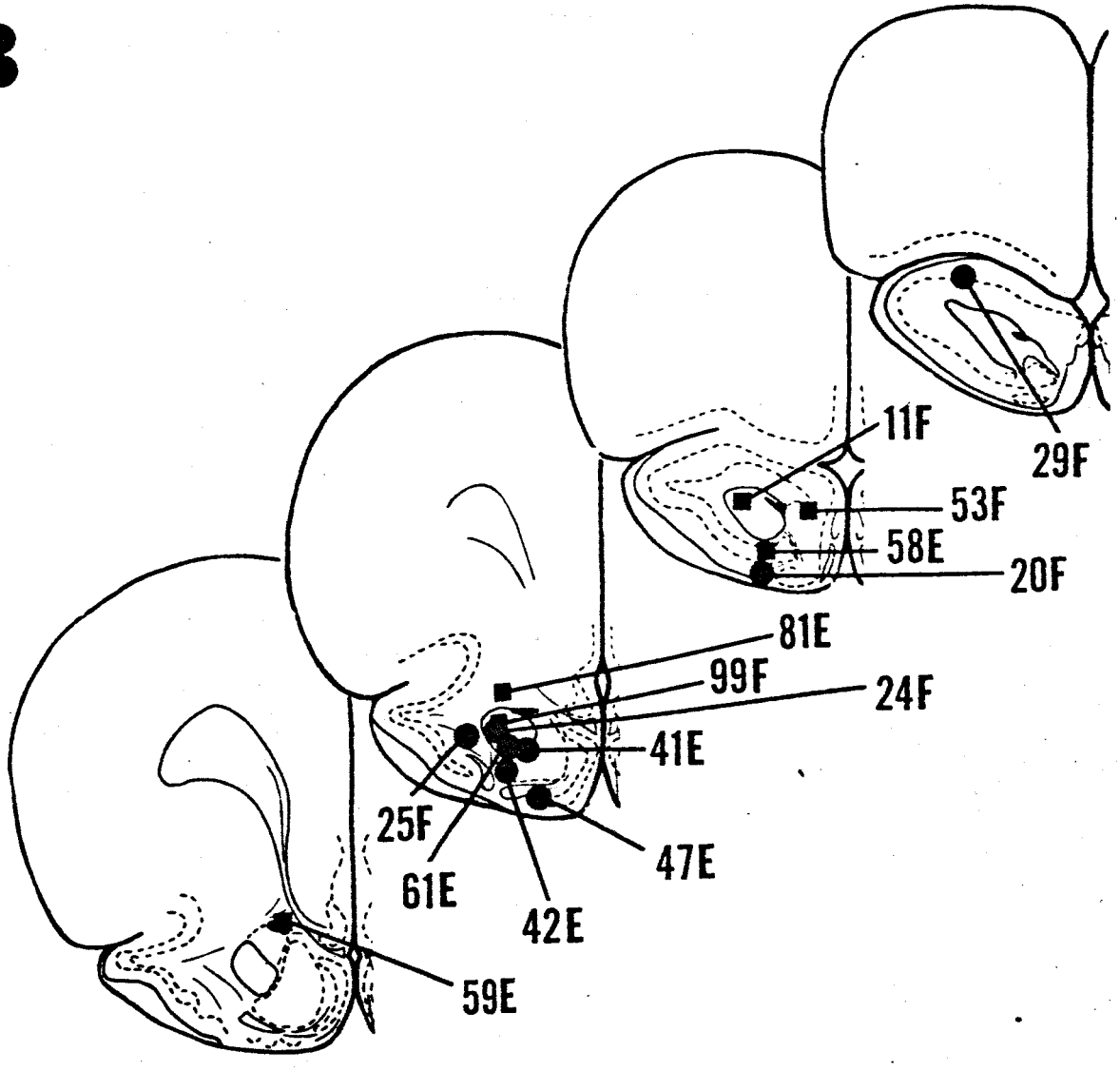

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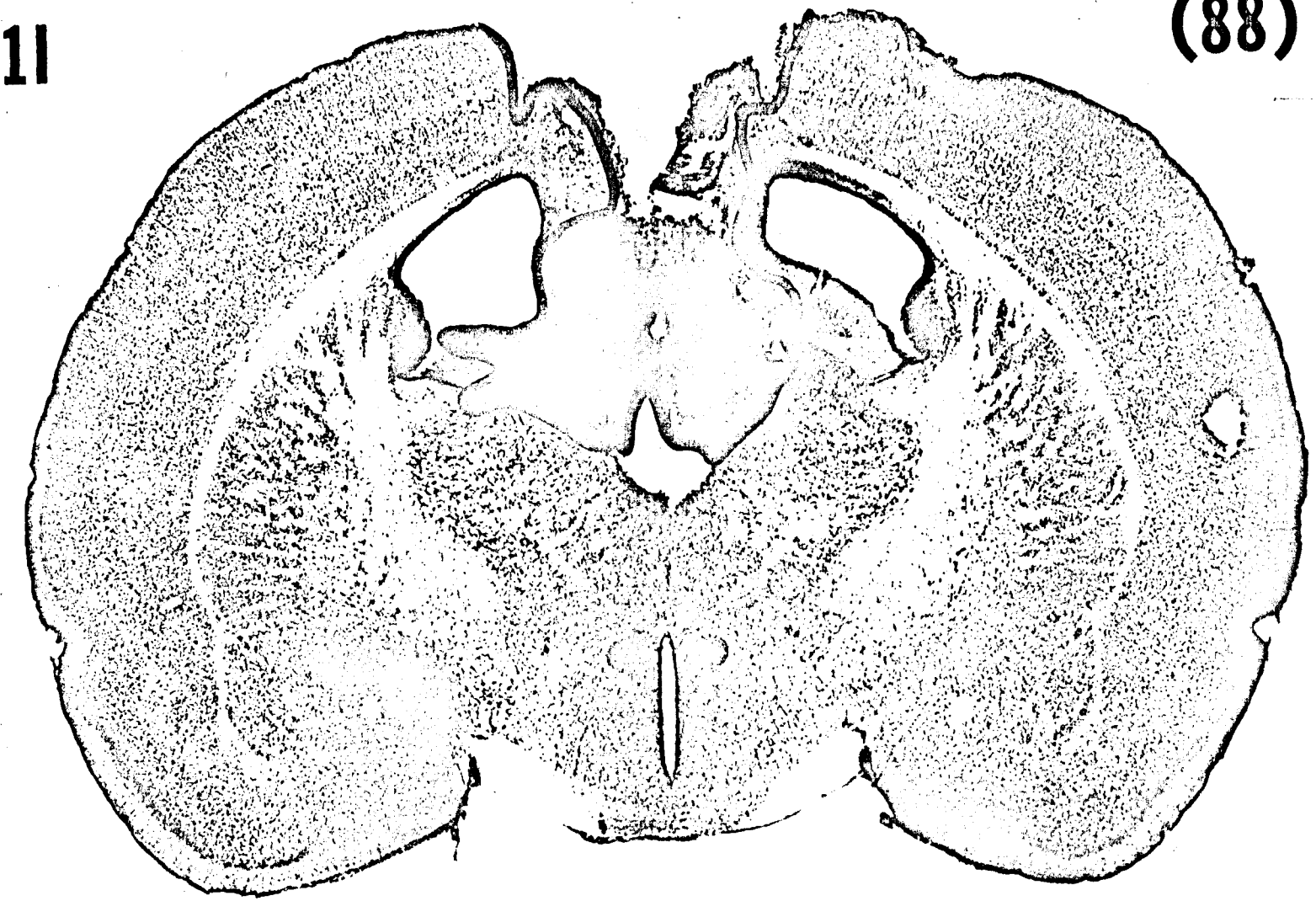

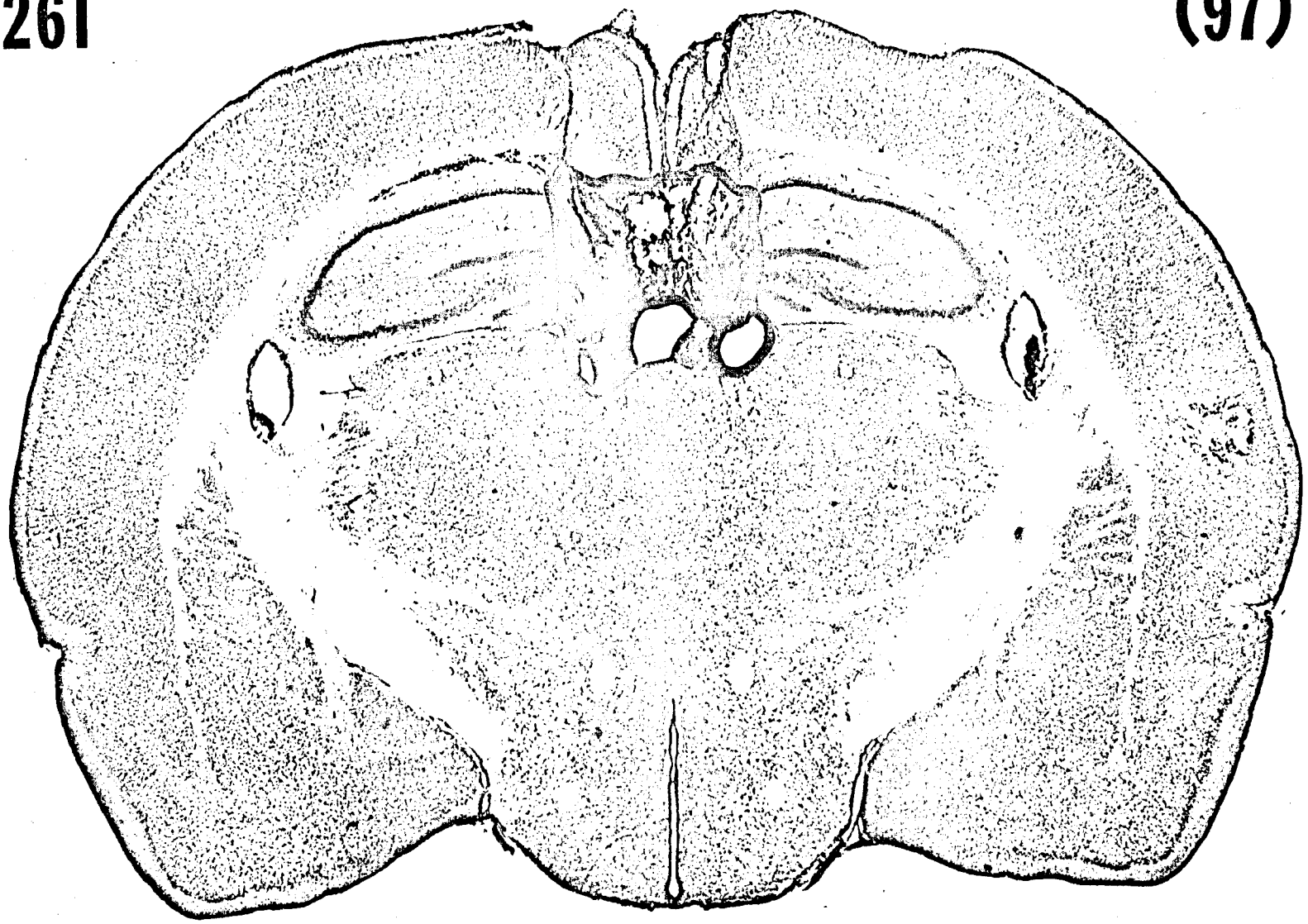

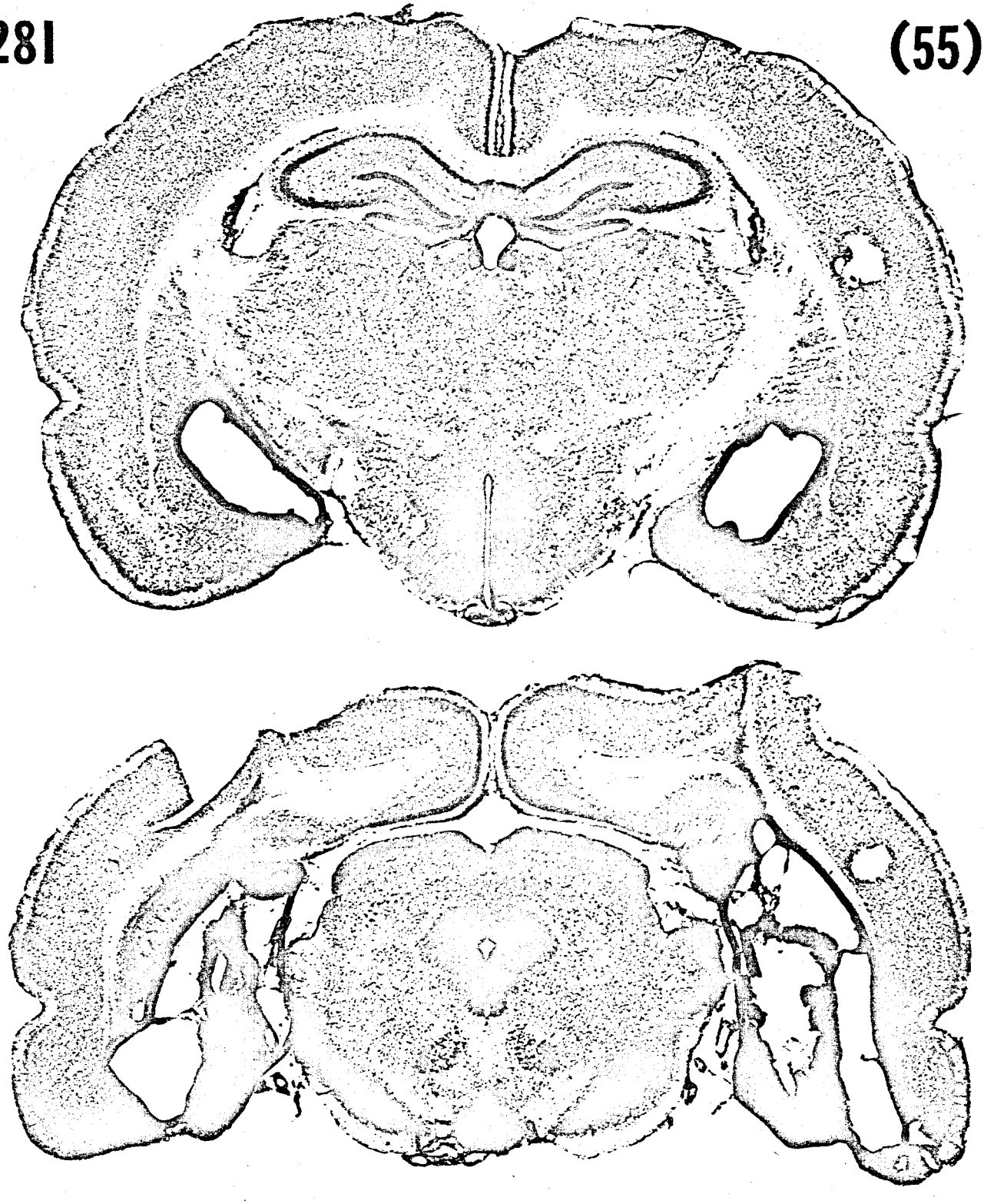

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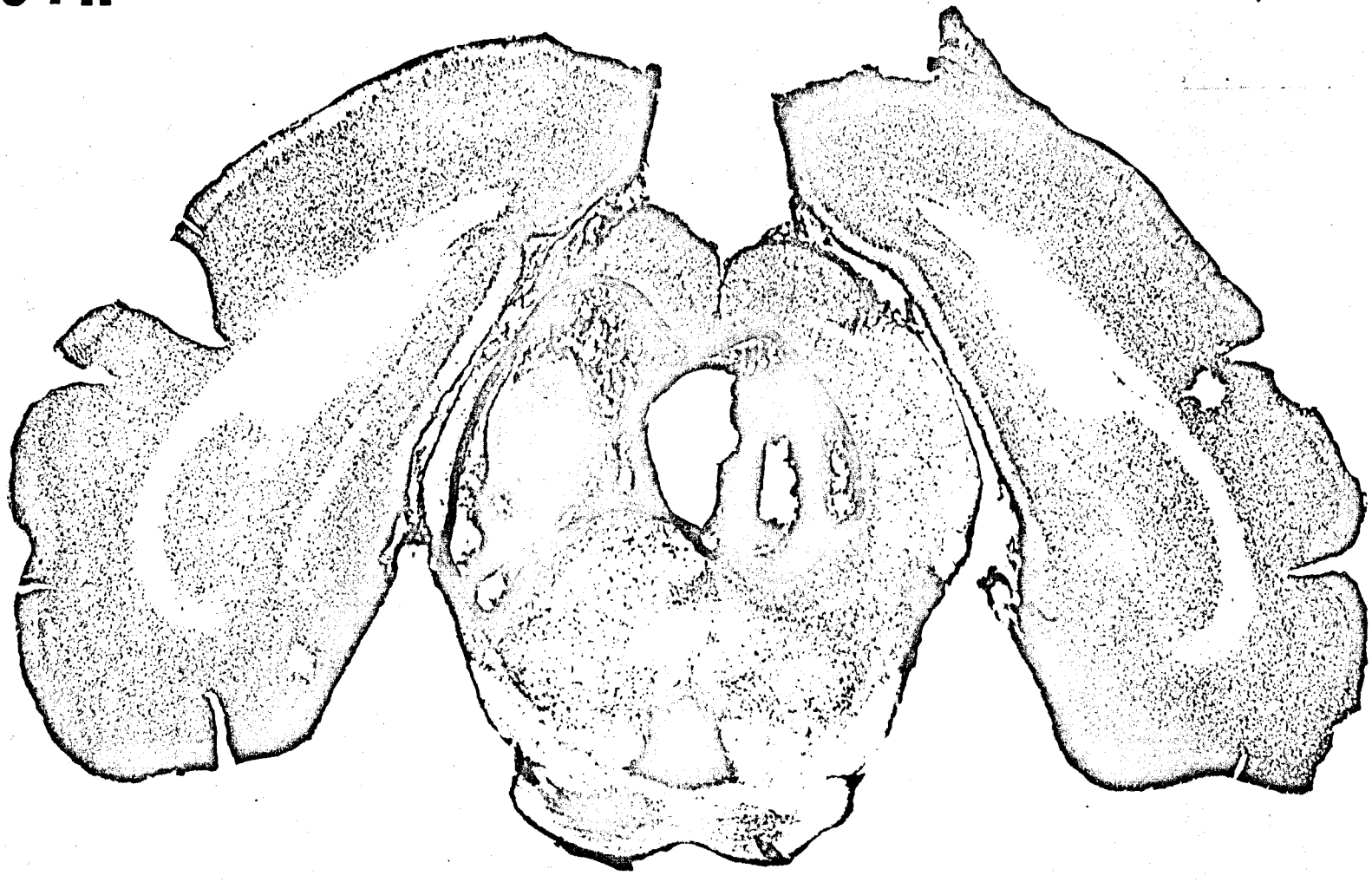

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